Original article

Ten-year retrospective review of clinical characteristics and treatment outcomes among Thai adult patients with Hodgkin lymphoma

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Abstract:

Introduction: *Among Thai patients, clinical characteristics and treatment outcomes in Hodgkin lymphoma remain limited. This study aimed to evaluate the clinical manifestations and treatment outcomes of adult patients with Hodgkin lymphoma.* ***Methods:*** *A retrospective study was conducted on adult patients with Hodgkin lymphoma at Srinagarind Hospital. Clinical characteristics and potential clinical risk factors for Hodgkin lymphoma outcomes were collected. Clinical predictive factors and overall survival were demonstrated using Cox regression analysis and Kaplan-Meier curves.* ***Results:*** *In a total of 84 patients, the median aged was 46.2 years old. The most common subtype of classical Hodgkin lymphoma was nodular sclerosis (33, 39.2%) and mixed cellularity (33, 39.2%). Most patients were stage II (31, 36.9%), and more than one half had constitutional symptoms (44, 52.4%). Complete remission was significantly associated with improved overall survival according to hazard ratio (HR) analysis (HR 0.4, p-value < 0.001). A significant association between poor overall survival and the existence of disease involvement in at least 3 sites was found (HR 1.8, p-value < 0.014). Those with early stage cancer had a greater overall survival rate than patients with advanced stage, according to Kaplan-Meier curves.* ***Conclusion:*** *In this study, mixed cellularity and nodular sclerosis were the two most common subtypes of Hodgkin lymphoma. The most common first line therapy was ABVD. Achieved complete remission was a protective factor associated with better survival. The presence of disease involvement in at least 3 sites was a substantial risk factor for poor outcomes.*

Keywords : ● *Hodgkin lymphoma* ● *Clinical predictive factors* ● *Overall survival*

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นิพนธ์ต้นฉบับ

การศึกษาย้อนหลัง 10 ปีสำหรับลักษณะทางคลินิกและปัจจัยที่สัมพันธ์กับการตอบสนองต่อการรักษามะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กินในผู้ป่วยผู้ใหญ่ไทย

พิสาข์ พิพิธพร ณัฐติยา เตียวตระกูล ชินดล วานิชพงษ์พันธุ์ และ ธีรินทร์ ลาน้ำเที่ยง
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บทคัดย่อ

บทนำ *การศึกษาเกี่ยวกับลักษณะทางคลินิกและผลการตอบสนองต่อการรักษาของโรคนี้ในประเทศไทยยังมีอยู่น้อย การศึกษานี้จึงมีจุดประสงค์เพื่อศึกษาข้อมูลดังกล่าว* ***วิธีการ*** *เป็นการศึกษาย้อนหลังในผู้ป่วยผู้ใหญ่ที่เป็นมะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กินที่โรงพยาบาลศรีนครินทร์ มีการเก็บข้อมูลเกี่ยวกับลักษณะทางคลินิกของผู้ป่วยและปัจจัยที่อาจมีผลต่อผลการรักษาซึ่งจะนำมาวิเคราะห์ต่อด้วยวิธี Cox regression และ Kaplan-Meier* ***ผลการวิจัย*** *มีผู้ป่วย 84 ราย อายุเฉลี่ย 46.2 ปี ชนิดย่อยที่พบบ่อยสุดคือ nodular sclerosis (33, 39.2%) และ mixed cellularity (33, 39.2%) ผู้ป่วยส่วนใหญ่อยู่ในระยะที่สอง (31, 36.9%) ส่วนใหญ่มีอาการตามระบบ (44, 52.4%) พบว่าการได้รับการตอบสนองต่อการรักษาแบบสมบูรณ์มีความสัมพันธ์ต่อการรอดชีวิต hazard ratio 0.4, $p < 0.001$ และการที่มีรอยโรคตั้งแต่ 3 ตำแหน่งสัมพันธ์กับการเสียชีวิต hazard ratio 1.8, $p = 0.014$ และจาก Kaplan-Meier curves พบว่าการที่มีระยะโรคเป็นระยะต้นมีอัตราการรอดชีวิตสูงกว่าระยะลุกลาม* ***สรุป*** *ชนิดย่อยของมะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กินที่พบบ่อยที่สุดคือ nodular sclerosis และ mixed cellularity ซึ่งมักรักษาสูตรแรกด้วยยา ABVD และหากได้ผลการตอบสนองเป็นแบบสมบูรณ์จะทำให้มีโอกาสรอดชีวิตสูงขึ้น และการที่มีรอยโรคตั้งแต่ 3 ตำแหน่งสัมพันธ์กับการเสียชีวิตที่มากขึ้น*

คำสำคัญ : ● *มะเร็งต่อมน้ำเหลืองชนิดฮอดจ์กิน* ● *ปัจจัยที่มีผลต่อการรักษา* ● *อัตราการรอดชีวิต*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:49-57.

Introduction

Hodgkin lymphoma is a malignancy stemming from lymphocytes in the lymph node and the lymphatic system. It consists of two types, namely, classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).

The four subtypes of CHL include nodular sclerosis (NSCHL), mixed cellularity (MCCHL), lymphocyte-rich CHL (LRCHL) and lymphocyte-depleted CHL (LDCHL).

The majority of patients are CHL, and the prevalence of each subtype varies depending on the nation, age, sex, nationality and socio-economic status. In the US, Europe and developed countries, HL was detected in around 10% of lymphomas and 0.6% of all malignancies. The incidence of HL is 2 to 3 per 100,000 people, and the prevalence of each subtype is 70% for NSCHL, 20 to 25% for MCCHL, 5% for LRCHL and 1% for LDCHL[1].

Few statistics have established Hodgkin lymphoma prevalence among Thai patients. From 2007 to 2014, the Thai lymphoma registry reported that 316 of 4,371 patients with newly diagnosed lymphoma had HL[31]. Cervical lymphadenopathy with slow progression to adjacent lymph nodes is a common clinical characteristic of CHL (60%). Only a small percentage presented solitary subdiaphragmatic lymphadenopathy[2]. The lymph node had a firm consistency and was not painful[3]. Patients frequently presented constitutional symptoms. The other clinical symptoms that brought the patient to the doctor included mediastinal mass and abdominal pain[4]. Although uncommon, patients with bone marrow involvement at first presentation have a worse prognosis[5].

The EBV virus, which is typically associated with mixed cellularity and lymphocyte depleted subtypes, is also frequently found among patients with HIV. Socio-economic status is an additional risk factor. In developed countries, HL is commonly found among late adolescents to younger adults and the elderly. On the contrary, it has been frequently found in childhood and older adults in developing countries[7-9]. Mixed cellularity and lymphocyte-depleted are the two most prevalent subtypes in underdeveloped countries. These findings could be attributed to the rising rates of HIV and EBV. Some research showed obesity and high sugar intake may be risk factors for HL[10]. Additionally, some research indicated that smoking increases the incidence of HL, although taking aspirin may be a protective factor for preventing disease due to the reduced NF-kB signal[11]. HL may develop after immunosuppression[12,13]. According to several research studies, auto-immune illnesses such as psoriasis, polyarthritis nodosa, polymyositis, Behcet's disease and Sjogren's syndrome are risk factors for developing this condition[14,15]. Having HL in the family could be a clinical risk factor for HL[16].

The treatment option is determined by the Lugano stage and clinical risk status. Clinical risk predicting scores from the German Hodgkin Study Group (GHSG) and European Organization for the Research and Treatment of Cancer (EORTC) are frequently used in the early stages (stages I and II) of cancer. When one of these conditions is present [age > 50, mediastinal mass >1/3 of the thoracic cavity at T5–6, ESR > 30 (B symptoms) or > 50 (no B symptoms), location of involvement at least four sites] the EORTC score will indicate unfavorable risk. When one of these conditions is present [age > 50, mediastinal mass > 1/3 of the thoracic cavity (T5-6 level), ESR > 30 (B symptoms) or > 50 (no B symptoms), location of involvement at least three sites] the German Hodgkin Study Group (GHSG) will determine that the risk is unfavorable. However, this criterion differs from the EORTC regarding the site of involvement in that it requires at least three sites to be involved. The primary treatment for early-stage (stages I to II) cancer is multimodality, including chemotherapy and radiation. Depending on the clinical risk category and the applications of PET scans, the choice of chemotherapy is determined. When the protocol is PET-guided therapy, the chemotherapy regimen will change to escalated BEACOPP if the PET scan following the second cycle of ABVD is positive, and radiation will follow chemotherapy when it has been finished. This will result in

5-year relapse-free survival (RFS) of greater than 90% and 5-year overall survival (OS) of greater than 95%[18,19]. In the advanced stages (stages III to IV), the main treatment is chemotherapy, which may be combined with radiotherapy when the initial mass is bulky or when the disease still persists after chemotherapy[17]. Most often, the ABVD regimen is still used as the first line of treatment because other regimens, such as escalating BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) or Stanford V, may increase survival but also increase toxicity[20-22]. The BV-AVD regimen appears to be a good regimen for the advanced stage; however, the cost is prohibitive[21]. Regarding the International Prognostic Score, a prognostic index for advanced stages, includes serum albumin levels below 4 g/dL, hemoglobin levels below 10.5 g/dL, male sex, age greater than 45 years, stage IV, WBC levels beyond 15,000 cell/uL, absolute lymphocyte counts below 600, or WBC counts below 8%, and each factor impacts PFS and OS[23]. Five years relapse-free survival rate of the advanced stage is 60 to 85%, and 5-year overall survival rates are 85-90%[24,25]. Chemosensitive relapsed or refractory disease can benefit from autologous hematopoietic stem cell transplantation.

Revised international working group (IWG) criteria are used to evaluate disease response to treatment, although their application in our country might be limited due to the high cost of PET scan.

There has been little research of the clinical characteristics and treatment outcomes of HL in Thailand, which may differ from those observed in Europe or the US. Therefore, we are interested in researching the clinical characteristics and treatment outcomes of these patients

Material and methods

We studied patients with Hodgkin lymphoma aged at least 18 years old visiting Srinagarind Hospital from January 2009 to January 2019.

The primary objective of this research aimed to define the clinical characteristic of patients with HL in Khon Kaen Province.

The secondary objective aimed to define factors affecting treatment outcomes and explore the treatment response of our patients over the last 10 years.

Statistical analysis

We described clinical characteristics of our patients using percentage for quantitative and qualitative data and Cox proportional hazard model to identify the possible factor affecting survival outcome both univariate and multivariate analysis with the significant level at $p = 0.05$. We also used Kaplan-Meier to analyze subtypes of Hodgkin lymphoma and staging affecting survival outcome.

Results

A total of 86 patients with Hodgkin lymphoma were compatible with our inclusion criteria and data could be analyzed.

Baseline characteristics of our patients consisted of males predominantly; the median age was 46.2±24.7 years old. The most common subtypes of Hodgkin lymphoma were NSCHL and MCCHL equally followed by NLPHL and the least common was LRCHL and LDCHL. Most patients were stage II followed by stage IV, stage III and the least common was stage I. More than one half of the patients had constitutional symptoms such as fever, weight loss and loss of appetite. Most patients had disease involvement in less than three sites and most had the nonbulky disease and did not have bone marrow involvement. Almost 60% of patients received Dacarbazine containing regimens and common chemotherapy regimens were the ABVD regimen, followed by ABV, CHOP, and palliative regimen (steroid, CP, best supportive care). The three least commonly used regimens were ABVD then escalated BEACODP (our center has not had procarbazine), followed by COPP alternated with ABV and COPP that were used equally.

The rate of patients that were treated with radiotherapy and did not receive radiotherapy was equal. Most did not present febrile neutropenia during treatment. More than one half of the patients had complete response to chemotherapy, followed by partial response. Patients had refractory disease less than 10% (Table 1)

From multivariate analysis, the factors affecting survival were complete remission HR = 0.45 ($p < 0.005$, 95%CI: 0.27-0.74) and more than three sites were involved HR = 1.91 ($p = 0.005$, 95%CI: 1.22-2.98) while advanced stage could be a risk factor affecting survival but without statistical significance (Table 2)

From Kaplan-Meier analysis, we found early stage disease (stages I and II) was a better prognosis than those from patients with advanced stage (stages III and IV) (Figure 1). The NSCHL and NLPHL subtype indicated the best prognosis, while the LDCHL subtype revealed the worst prognosis (Figure 2).

Table 1 Baseline characteristics of patients

Characteristic	Patients (n = 84)
Mean age ± SD, years (at enrollment)	46.2 ± 24.7
Sex, n (%)	
Female	41 (48.8)
Male	43 (51.2)
Immunosuppressant, n (%)	1 (1.2)
Autoimmune disease, n (%)	3 (3.6)
Family history of cancer, n (%)	4 (4.8)
Smoking, n (%)	14 (16.7)
BMI >25, n (%)	16 (19.0)
ASA used, n (%)	2 (2.4)
Cell type, n (%)	
NSCHL	33 (39.2)
mixed cellularity	33 (39.2)
LRCHL	4 (4.8)
LDCHL	4 (4.8)
NLPHL	10 (12.0)
Stage, n (%)	
I	10 (12.0)
II	31 (36.8)
III	19 (22.6)
IV	24 (28.6)
B symptoms, n (%)	44 (52.4)
Involved ≥ 3 sites, n (%)	37 (44.0)
Bulky mass, n (%)	31 (36.9)
Mediastinal mass >1/3, n (%)	12 (14.3)
Bone marrow involvement, n (%)	9 (10.7)
Chemotherapy regimen, n (%)	
ABVD	47 (56.0)
ABVD then escBEACODP	2 (2.4)
ABV	22 (26.2)
COPP/ABV	2 (2.4)
COPP	2 (2.4)
CHOP	4 (4.8)
Steroid or CP or BSC	5 (6.0)
Dacarbazine containing regimen, n (%)	49 (58)
Radiotherapy, n (%)	41 (48.8)
Early stage receiving RT, n (%)	24/41 (58.5)
Advanced stage receiving RT, n (%)	17/43 (39.5)
Febrile neutropenia, n (%)	6 (7.1)
Treatment response, n (%)	
Complete remission	55 (65.5)
Partial response	20 (23.8)
Stable disease	4 (4.8)
Progressive disease	3 (3.6)
Unknown (loss follow up)	2 (2.4)
Mean hemoglobin ± SD, g/dL	12.0 ± 2.0
Mean white blood cell ± SD, cell/uL	11,003 ± 5840
Mean absolute lymphocyte count ± SD, cell/uL	2346.7 ± 1737.9
Mean ESR ± SD, mm/hr	57.3 ± 36.4
Mean LDH ± SD, U/L	244.8 ± 81.9
Mean albumin ± SD, g/dL	4.0 ± 0.6

Discussion

We found our results concordant with a related study of Thai Lymphoma Study Group Registry including median age, predominant sex and common cell type of Hodgkin lymphoma[31]. Our center's accessibility to dacarbazine was similar to that of overall Thai patients[31]

Complete response was associated with better long term survival. This result might have been due to a low residual tumor, and tumor involvement at least three sites were associated with the worst outcomes from both univariate and multivariate analyses. These findings were consistent with the German Hodgkin Study Group[29]. Our results found that advanced stage was another strong risk factor affecting survival about three times that of early stage but not statistically significant possibly due to insufficient patients.

Early stage disease (stages I and II) proved a better prognosis than advanced stage (stages III and IV) (Figure 1.) that was consistent with related studies, also in overall Thai population[29-31].

Table 2 Multivariate analysis of risk factors for death

Variable	HR	95%CI	*p*-value
Involvement ≥ 3 sites	1.83	1.13-2.97	0.01
Complete remission	0.45	0.26-0.78	0.00
RT	0.96	0.56-1.64	0.87
ASA used	1.65	0.20-13.51	0.64
Immunosuppressant	2.72	0.15-49.96	0.50
Advanced stage	2.66	0.93-7.63	0.069
Bulky mass	0.59	0.33-1.07	0.08

Abbreviation: HR, hazard ratio; 95%CI, 95% confidence interval

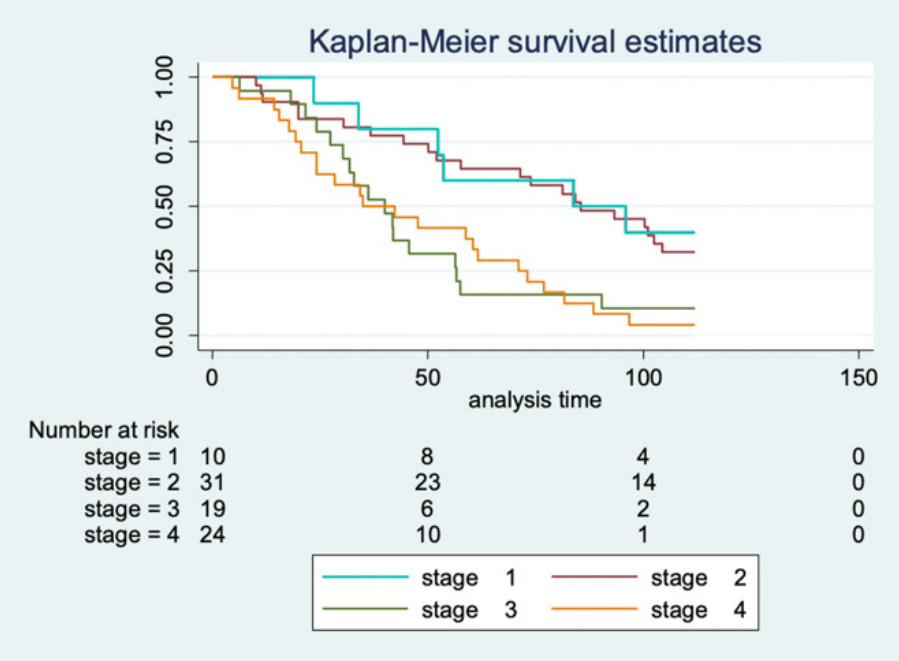

Figure 1 Overall survival of patients with Hodgkin lymphoma by stage

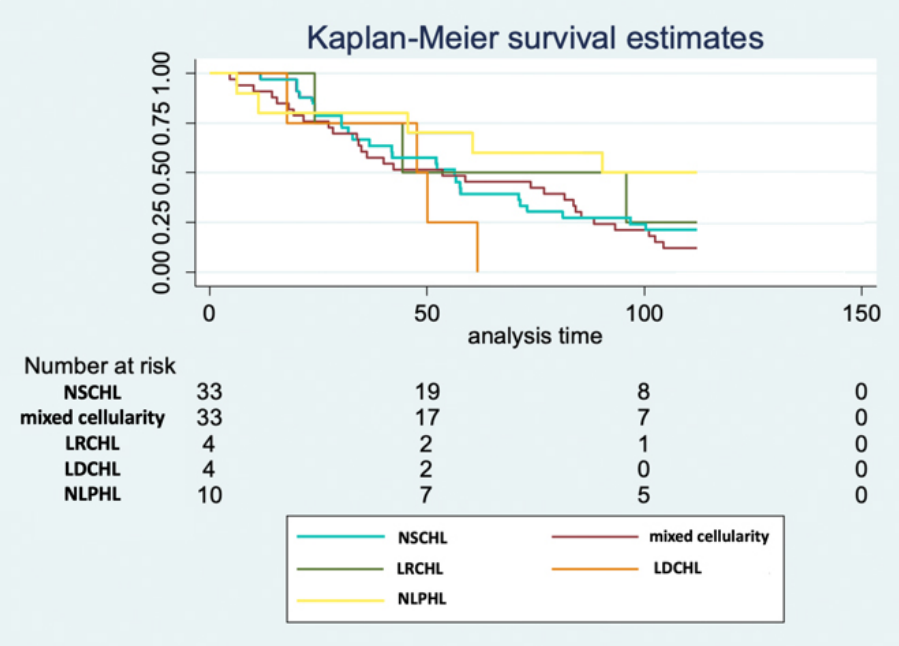

Figure 2 Overall survival of patients with Hodgkin lymphoma by subtype

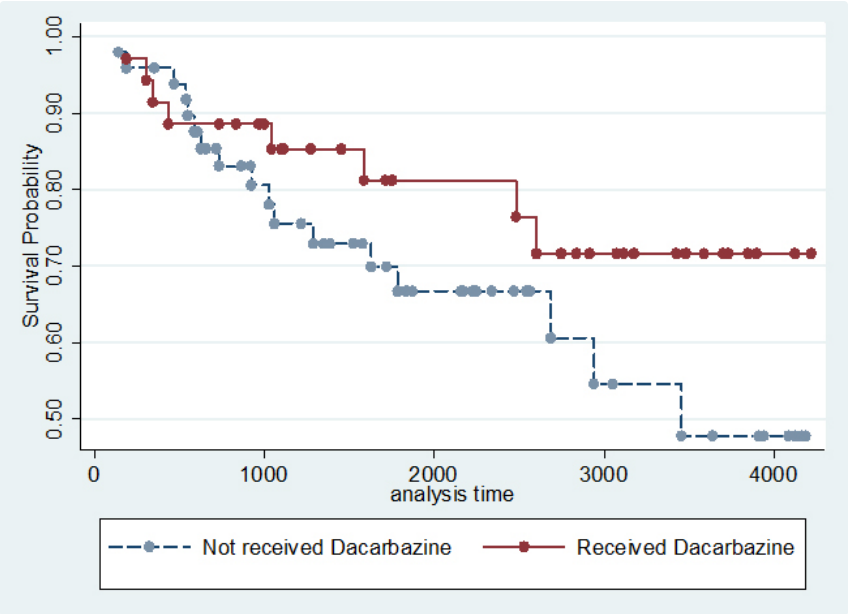

Figure 3 Overall survival of patients with Hodgkin lymphoma by dacarbazine receiving status

NSCHL and NLPHL subtypes had the best prognosis (Figure 2), which was consistent with the nature of their diseases. In contrast, our data revealed the LDCHL subtype had the worst prognosis[31], which was consistent with the WHO data. This could be because this subtype is frequently found among immunocompromised hosts, increasing the risk of infection. In this study, the patients were males and females equally, and most were NSCHL which was similar to a related study[1].

ABVD is a standard chemotherapy regimen. However, some patients did not receive dacarbazine in the past because of public health insurance, which might be one of the reasons our patients' treatment outcomes did not compare favorably with those of developed countries[18,19] (Figure 2) because receiving dacarbazine constituted a potential factor that could improve treatment outcome, as demonstrated by our study (Figure 3) and that of the Thai Lymphoma Study Group[31]. Additionally, due to the expensive cost of PET scans, only a small number of patients could afford them[27]. These showed limitations of Hodgkin lymphoma treatment in Thailand.

Although limited resources exist, the febrile neutropenia rate due to treatment was low suggesting that prescribing G-CSF as primary prophylaxis in these regimens was unnecessary which was similar to standard guidelines[28].

Our study encountered limitations. First, we did not separately analyze factors that might have affected overall survival in the early and advanced stages, as these might differ between cancer stage. Another limitation was the study employed a retrospective design.

Conclusion

Patients with Hodgkin lymphoma in Khon Kaen Province were commonly found in younger age and male predominant groups similar to those worldwide. Nodular sclerosis and mixed cellularity were the most common subtypes of Hodgkin lymphoma in this study. ABVD was the most common first -line treatment. More than one half could achieve complete remission after chemotherapy and this proved a protective factor associated with better survival. The presence of disease involvement in at least three sites was a significant risk factor associated with poor outcomes.

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References

1. Stein H, Pileri SA, Weiss LM, Poppema S, Gascoyne RD, Jaffe ES. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 2017. p. 424-42
2. Connors JM. Clinical Manifestations and Natural History of Hodgkin's Lymphoma. The Cancer Journal. 2009;15:124-8.
3. Peters MV, Alison RE, Bush RS. Natural history of Hodgkin's disease as related to staging. Cancer. 1966;19:308-16.
4. Cervantes F, Briones J, Bruguera M, Font C, Grau J-M, Rozman C, et al. Hodgkin's disease presenting as a cholestatic febrile illness: incidence and main characteristics in a series of 421 patients. Annals of Hematology. 1996;72:357-60.
5. Howell SJ, Grey M, Chang J, Morgenstern GR, Cowan RA, Deakin DP, et al. The value of bone marrow examination in the staging of Hodgkin's lymphoma: a review of 955 cases seen in a regional cancer centre. Br J Haematol. 2002;119:408-11.
6. Hummel M, Anagnostopoulos I, Dallenbach F, Korbjuhn P, Dimmler C, Stein H. EBV infection patterns in Hodgkin's disease and normal lymphoid tissue: expression and cellular localization of EBV gene products. British Journal of Haematology. 1992;82:689-94.
7. Ferreira JM de O, Klumb CE, Reis R de S, Santos M de O, Oliveira JFP, de Camargo B, et al. Lymphoma subtype incidence rates in children and adolescents: First report from Brazil. Cancer Epidemiology. 2012;36:e221-6.
8. Barros MHM, Hassan R, Niedobitek G. Disease patterns in pediatric classical Hodgkin lymphoma: a report from a developing area in Brazil. Hematol Oncol. 2011;29:190-5.
9. Correa P, O'Conor GT. Epidemiologic patterns of Hodgkin's Disease. Int J Cancer. 1971;8:192-201.
10. Epstein MM, Chang ET, Zhang Y, Fung TT, Batista JL, Ambinder RF, et al. Dietary Pattern and Risk of Hodgkin Lymphoma in a Population-Based Case-Control Study. Am J Epidemiol. 2015;182:405-16.
11. Castillo JJ, Dalia S, Shum H. Meta-Analysis of the Association Between Cigarette Smoking and Incidence of Hodgkin's Lymphoma. JCO. 2011;29:3900-6.
12. Garnier JL, Lebranchu Y, Dantal J, Bedrossian J, Cahen R, Assouline D, Jaccard A, Fetissoff F, Moreau A, Martin X, Delsol G, Berger F, Touraine JL. Hodgkin's disease after transplantation. Transplantation. 1996;61:71-6.
13. Dal Maso L, Franceschi S, Polesel J, Braga C, Piselli P, Crocetti E, et al. Risk of cancer in persons with AIDS in Italy, 1985-1998. Br J Cancer. 2003;89:94-100.
14. Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Hodgkin lymphoma after autoimmune diseases by age at diagnosis and histological subtype. Annals of Oncology. 2014;25:1397-404.
15. Landgren O, Engels EA, Pfeiffer RM, Gridley G, Mellemkjaer L, Olsen JH, et al. Autoimmunity and Susceptibility to Hodgkin Lymphoma: A Population-Based Case-Control Study in Scandinavia. JNCI: Journal of the National Cancer Institute. 2006;98:1321-30.
16. Goldin LR, Pfeiffer RM, Gridley G, Gail MH, Li X, Mellemkjaer L, et al. Familial aggregation of Hodgkin lymphoma and related tumors. Cancer. 2004;100:1902-8.
17. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:iv19-29.
18. Fermé C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, et al. Chemotherapy plus Involved-Field Radiation in Early-Stage Hodgkin's Disease. N Engl J Med. 2007;357:1916-27.
19. Sjoberg J, Halthur C, Kristinsson SY, Landgren O, Axdorph Nygell U, Dickman PW, et al. Progress in Hodgkin lymphoma: a population-based study on patients diagnosed in Sweden from 1973-2009. Blood. 2012;119:990-6.
20. Fermé C, Thomas J, Brice P, Casasnovas O, Vranovsky A, Bologna S, et al. ABVD or BEACOP baseline along with involved-field radiotherapy in early-stage Hodgkin Lymphoma with risk factors: Results of the European Organisation for Research and Treatment of Cancer (EORTC-Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. European Journal of Cancer. 2017;81:45-55.
21. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2018;378:331-44.
22. Chisesi T, Bellei M, Luminari S, Montanini A, Marcheselli L, Levis A, et al. Long-Term Follow-Up Analysis of HD9601 Trial Comparing ABVD Versus Stanford V Versus MOPP/EBV/CAD in Patients With Newly Diagnosed Advanced-Stage Hodgkin's Lymphoma: A Study From the Intergruppo Italiano Linfomi. JCO. 2011;29:4227-33.
23. Hadley TJ. A prognostic score for advanced Hodgkin's disease. Evidence-based Oncology. 2000;1:12-3.
24. Aleman BMP, Raemaekers JMM, Tirelli U, Bortolus R, van 't Veer MB, Lybeert MLM, et al. Involved-Field Radiotherapy for Advanced Hodgkin's Lymphoma. N Engl J Med. 2003;348:2396-406.
25. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003;348:2386-95. Erratum in: N Engl J Med. 2005;353:744.
26. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised Response Criteria for Malignant Lymphoma. JCO. 2007;25:579-86.
27. André MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early Positron Emission Tomography Response-Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. JCO. 2017;35:1786-94.

28. *Vakkalanka B, Link BK. Neutropenia and Neutropenic Complications in ABVD Chemotherapy for Hodgkin Lymphoma. Advances in Hematology. 2011;2011:1-7.*
29. *Klimm B, Goergen H, Fuchs M, von Tresckow B, Böll B, Meissner J, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. Annals of Oncology. 2013;24:3070-6.*
30. *Qi S, Milgrom S, Dabaja B, Tsang R, Levis M, Ricardi U, et al. Two distinct prognostic groups in advanced-stage Hodgkin lymphoma revealed by the presence and site of bulky disease. Blood Advances. 2020;4:2064-72.*
31. *Suwanban T, Nakhakes C, Lekhakula A, Julamanee J, Norasetthada L, Nawarawong W, et al. Treating Hodgkin Lymphoma without Dacarbazine: a Lesson Learned from Thailand. Blood. 2015 Dec 3;126(23):5002-5002.*